PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IN 02/00131	International filing date *(day/month/year)* 13.06.2002	Priority date *(day/month/year)* 26.03.2002
International Patent Classification (IPC) or both national classification and IPC C07C213/02		
Applicant GLOBAL BULK DRUGS &FINE CHEMICALS PVT. LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.10.2003	26.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, M Telephone No. +49 89 2399-8335

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 02/00131

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-5, 8-17	as originally filed
7 ✓	filed with telefax on 21.09.2004
6 ✓	received on 14.10.2004 with letter of 09.10.2004

Claims, Numbers

1-12 ✓	received on 14.10.2004 with letter of 09.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

D1 US 6 350 912
D2 US 2 462 736
D3 US 4 535 186 cited in the present demand.
D4 W. E. Fristad *et al.*, J. Org. Chem., 50(17) 3413-3148 (1985)
D5 letter of 08.09.2004 from Monarch Catalyst Pvt. Ltd

1. Amendments - Art.34(2)b) PCT

1.1 The present application has been restricted to the preparation of the phenylethylamine derivative of Formula (II) starting from the nitrile equivalent of Formula (I) by reduction with Raney Nickel of type CORMIII.

1.2 The bulk density, Ni composition and nitrobenzene activity are based on a technical specification document provided by the applicant in his fax of 21.09.2004 (cf. **D5**).

All these modifications satisfy to the requirements of article 34(2)b) PCT.

2. Novelty - Art. 33(2) PCT

D1 relates to the one pot [illegible] of venlafaxine comprising the reduction of the corresponding cyano-derivative with a formylating agent in a protic solvent, i.e. methanol, in the presence of a catalyst, i.e. Raney Ni, at a temperature in the range of 30-60°C, at pressure between 100-400 psi for 6-16 hours.

D2 describes the preparation of N,N'-dimethylethanolamine by hydrogenation of the formaldehyde cynahydrin in the presence of formyldehyde in methanol with a Raney Ni catalyst at temperatures between 15-150°C and pressures between 200-700atm.

Syntheses of venlafaxine (a) by condensation of p-methoxyphenylacetonitrile with cyclohexanone, followed (b) by the catalytic hydrogenation over Rh/Al_2O_3 and (c) N-methylation according to the Eschweiler-Clarke are known from the prior art, for instance from **D3** (a) -70°C in THF, nBuLi/hexane; (b) in an ammonia-ethanol solution.

D4 discloses a general procedure for the hydrogenation of α-cyano lactones (page 3148, lines 27-41).

None of the above-cited documents relate to the preparation of compound of Formula (II) from compound of Formula (I) by reductive treatment with Raney Nickel of type CORMIII.

Novelty could be recognized for the process according to claims 1-12.

3. Inventive step - Art. 33(3) PCT

The closest prior art related process is known from document **D3** (col.3, lines 32-60; examples 2, 5, 10). It differs from the one of the present application by the catalyst used: Rh/Al_2O_3 or $LiAlH_4$ instead of Raney Nickel of type CORMIII. The present technical problem is to propose an improved manufacture process of phenyl ethylamine compound of Formula II. It is already known from **D1**, **D2** or **D4**, that Raney Ni catalyst in combination with the ammonia-ethanol solvent system are useful in the hydrogenation procedure of cyano-derivatives. The present application has proven by comparative examples that the type of Raney Nickel used has a dramatic influence on the recovery of the final amino product (pages 11-12; Tables II and III). This technical feature was never investigated in the prior art and here is proven to be of considerable industrial value. Accordingly an inventive step would be acknowledged for the process according to claims 1-12.

4. Comments:

4.1 The [illegible]g given for the patent EP 0112338A2 on page 3 of the present demand is [illegible]

4.2 Quite a few structures of the present demand are misleading or inconsistent with the present subject-matter:

- the cyano derivative of formula (I) is missing the hydrogen on the hydroxy group throughout the description;
- The formula V on page 4 and formula (VII) on page 10 are unreadable/incomplete.

4.3 The documents cited on page 4, lines 23-24 do not refer to the reduction conditions indicated in these documents, Rh is used therein as a catalyst not Raney Ni. The passage in the description from page 4, line 22 to page 5, line 7 is accordingly confusing (Art. 6 PCT).

4.4 The unit of pressure expressed in and throughout the description and claims does not meet the requirements of Rule 10.1(a) PCT and should have been replaced by the appropriate SI unit.

In the present system the required amine of formula V is produced at a better yield than that described in the prior art and at the same time there is provided a system which can be handled in a safer way as the system involves no hazardous chemicals and the reduction at pressure of 120 psi of hydrogen is a safer process at which the inventor carried out successful hydrogenation.

In the present invention the methylation of the amine to dimethyl amine has also been optimized.

OBJECTS

The main objective of the present invention is to produce phenyl ethyl compound of formula II and derivative thereof by an optimised process of reduction through the use of a novel solvent combination which will reduce the cyanocarbinol most effectively.

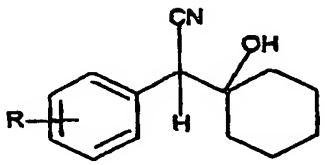
A further objective of the present invention is to provide a safe method of reducing the cyano methyl carbinol of fomula IV to amino ethyl carbinol of formula V.

It is yet another objective of the present invention to provide a method for methylating the said amine to the corresponding dimethyl derivative.

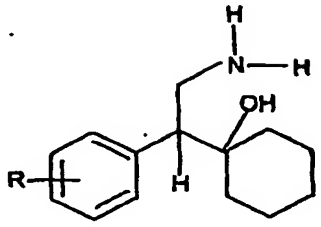
SUMMARY OF INVENTION

A process for preparation of hydroxy (cycloalkane) phenyl ethyl amine (Formula II) by reduction of cyano compound of formula 1 using Raney Nickel CORM III having bulk density between 0.50 to 0.60 gm/cc as catalyst

FPAA/167 (PCT)



Formula I



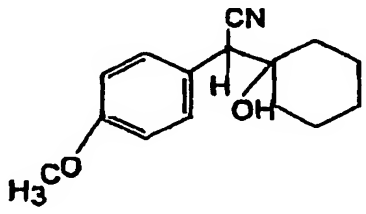
Formula II

where, R is in meta or para position and independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, amino, alkyl amino, alkaneamido, halo and triflouro methyl.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the process for safe manufacture of [illegible]1-[p-methoxyphenyl)ethyl]cyclohexanol of formula V and met[illegible]mpound of formula V to the compound 1-[2-dimethyl (p-methoxypr[illegible]xanol of formula VI .

In formula I when either R5 or R6 is in para position and either one of them is -OCH3 and the other is H, R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol

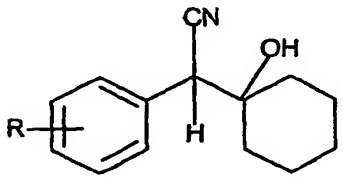


Formula IV

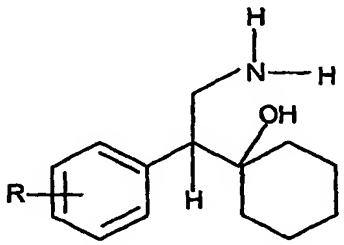
FPAA/167 (PCT)

CLAIMS:

1. Process for preparation of hydroxy (cycloalkane) phenyl ethyl amine (Formula II) by reduction of cyano compound of formula 1 using Raney Nickel CORM III having bulk density between 0.50 to 0.60 gm/cc as catalyst



Formula I



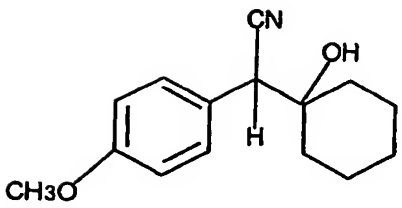
Formula II

where, R is in meta or para position and independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, amino, alkaneamido, halo and triflouro methyl.

2. Process according to claim 1, wherein said Raney Nickel comprises 86 to 88 wt% Nickel.

3. Process according to any of claims 1 or 2, wherein said Raney Nickel has nitrobenzene activity between 55 – 65 ml. /gm. / min of Hydrogen.

4. Process according to claim 1, wherein R is in para position and is $-OCH_3$ and the compound of formula 1 is 1-[cyano-(p-methoxyphenyl)methyl]cyclohexanol, a compound of formula III.



Formula III

5. Process according to claim 1, wherein said reduction is carried out in solvent of aqueous ammonia and methanol.

6. Process according to claim 1, wherein said reduction is carried out at temperature between -5 to 40^{0}C.

7. Process according to claim 6, wherein said temperature is between 15 to 30^{0}C.

8. Process according to claim 7, wherein said temperature is 27^{0}C.

9. Process according to any of the preceding claims, wherein said reduction is carried out for a period of 24 hours.

10. Process according to claim 9, wherein said reduction is carried out for a period of 8 to 24^{0}C.

11. Process according to claim 10, wherein said reduction is carried out for a period of 9 hours.

12. Process according to any of the preceding claims, wherein said reduction is carried out at a pressure of 120 psi of hydrogen.